FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

MESTRADO INTEGRADO EM MEDICINA

2013/2014

Iolanda Manuel Queirós Mendes Ribeiro Vieira

Vascular calcifications in an incident population of peritoneal dialysis patients

março, 2014

FACULDADE DE MEDICINA
UNIVERSIDADE DO PORTO

Iolanda Manuel Queirós Mendes Ribeiro Vieira

Vascular calcifications in an incident population of peritoneal dialysis patients

Mestrado Integrado em Medicina

Área: Nefrologia

Trabalho efetuado sob a Orientação de:

Mestre Carla Alexandra Ribeiro dos Santos Araújo

Trabalho organizado de acordo com as normas da revista:

Portuguese Journal of Nephrology and Hypertension

março, 2014

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO
UNIDADE CURRICULAR PROJETO DE OPÇÃO DISSERTAÇÃO / MONOGRAFIA

Projeto de Opção do 6º ano - DECLARAÇÃO DE INTEGRIDADE

Eu, **Iolanda Manuel Queirós Mendes Ribeiro Vieira**, abaixo assinado, nº mecanográfico **200804445**, estudante do 6º ano do Ciclo de Estudos Integrado em Medicina, na Faculdade de Medicina da Universidade do Porto, declaro ter atuado com absoluta integridade na elaboração deste projeto de opção.

Neste sentido, confirmo que **NÃO** incorri em plágio (ato pelo qual um indivíduo, mesmo por omissão, assume a autoria de um determinado trabalho intelectual, ou partes dele). Mais declaro que todas as frases que retirei de trabalhos anteriores pertencentes a outros autores, foram referenciadas, ou redigidas com novas palavras, tendo colocado, neste caso, a citação da fonte bibliográfica.

Faculdade de Medicina da Universidade do Porto, 20/03/2014

Assinatura conforme cartão de identificação:

Iolanda Manuel Queirós Mendes Ribeiro Vieira

U.PORTO
FMUP FACULDADE DE MEDICINA UNIVERSIDADE DO PORTO
UNIDADE CURRICULAR PROJETO DE OPÇÃO DISSERTAÇÃO / MONOGRAFIA

Projecto de Opção do 6º ano – DECLARAÇÃO DE REPRODUÇÃO

NOME

Iolanda Manuel Queirós Mendes Ribeiro Vieira

CARTÃO DE CIDADÃO OU PASSAPORTE (se estrangeiro)	E-MAIL	TELEFONE OU TELEMÓVEL
13735339	mimed08105@med.up.pt	916157623

NÚMERO DE ESTUDANTE	DATA DE CONCLUSÃO
200804445	2014

DESIGNAÇÃO DA ÁREA DO PROJECTO

Nefrologia

TÍTULO DISSERTAÇÃO/MONOGRAFIA (riscar o que não interessa)

Vascular calcifications in an incident population of peritoneal dialysis patients

ORIENTADOR

Mestre Carla Alexandra Ribeiro dos Santos Araújo

COORIENTADOR (se aplicável)

É autorizada a reprodução integral desta Dissertação/~~Monografia~~ (riscar o que não interessa) para efeitos de investigação e de divulgação pedagógica, em programas e projectos coordenados pela FMUP.

Faculdade de Medicina da Universidade do Porto, 20 / 03 / 2014

Assinatura conforme cartão de identificação: Iolanda Manuel Queirós Mendes Ribeiro Vieira

Aos meus avós, mãe e irmã, a minha casa.

Vascular Calcifications in an Incident Population of Peritoneal Dialysis Patients

Calcificações Vasculares numa População Incidente de Doentes em Diálise Peritoneal

Iolanda Vieira[1], Carla Santos-Araújo[1,2], Manuel Pestana[1,2]

[1] Faculty of Medicine, University of Porto. Porto, Portugal.

[2] Nephrology Department, Hospital de São João. Porto, Portugal.

Address of the institution:

Faculdade de Medicina da Universidade do Porto – Hospital de S. João

Alameda Prof. Hernâni Monteiro, 4200–319 Porto, Portugal.

Corresponding author:

Iolanda Manuel Queirós Mendes Ribeiro Vieira

Rua da Devesa, nº 120, 4635 - 299 Marco de Canaveses, Portugal.

E-mail: med08105@med.up.pt

ABSTRACT

Background: Vascular calcification is an independent prognostic marker of morbidity and mortality in patients with chronic kidney disease on dialysis. However, since the previous studies included predominantly hemodialysis patients, limited information is available regarding the peritoneal dialysis population. Therefore, the aim of our study was to retrospectively evaluate an incident peritoneal dialysis population in order to identify factors associated with the prevalence and progression of vascular calcifications. **Subjects and Methods:** Incident peritoneal dialysis patients from 1 January 2009 to 31 December 2011 were included in the study. Vascular calcifications were assessed using the simplified score of Adragão based on plain radiographs of pelvis and hands. Patients with and without vascular calcifications were compared for demographic, clinical and biochemical variables. After 12 months, the patients were divided according to the presence or absence of vascular calcification progression and compared for the aforementioned variables. **Results:** Ninety-nine patients were included in the study. The population evaluated had a median age of 45 years and 64% were males. Patients with vascular calcifications at baseline (28%) were significantly older (p=0.002), had a higher prevalence of diabetes (p<0.001) and vascular disease (p=0.001), as well as higher glucose (p<0.001) and B-type natriuretic peptide (p=0.012) plasmatic levels. After 12 months, progression of vascular calcification was observed in 15 of the 75 patients reevaluated. Patients with vascular calcification progression presented higher phosphorus plasmatic levels (p=0.011) and calcium-phosphorus product (p=0.015), in comparison with their baseline registers. **Conclusions:** In our population of peritoneal dialysis patients, vascular calcification at dialysis initiation was mainly associated with classic cardiovascular markers, such as older age, diabetes and elevated B-type natriuretic peptide plasmatic levels, whereas progression of vascular calcification were significantly associated with the calcium-phosphorus metabolism

parameters, reinforcing the importance of an adequate mineral and bone disorder control in the long term management of these patients.

Key-words: Calcium-phosphorus metabolism; cardiovascular disease; peritoneal dialysis; vascular calcification.

RESUMO

Introdução: A calcificação vascular é um fator de prognóstico independente de morbilidade e mortalidade nos doentes com doença renal crónica em diálise. Os estudos realizados previamente incidiram predominantemente em doentes em hemodiálise, pelo que a informação disponível relativamente à população em diálise peritoneal é limitada. **Objetivos:** Avaliar retrospetivamente os fatores associados à presença e progressão das calcificações vasculares numa população incidente em diálise peritoneal. **Material e Métodos:** Foram incluídos no estudo os doentes incidentes em diálise peritoneal de janeiro de 2009 a dezembro de 2011. As calcificações vasculares foram avaliadas através do score simplificado de Adragão, recorrendo a radiografias simples da pelve e das mãos. Os doentes com e sem calcificações vasculares foram comparados relativamente a variáveis demográficas, clínicas e bioquímicas. Após 12 meses, os doentes foram divididos consoante a presença ou não de progressão da calcificação e comparados relativamente às variáveis previamente mencionadas. **Resultados:** Foram incluídos no estudo 99 doentes. A população avaliada tinha uma idade média de 45 anos e 62% eram do sexo masculino. Os doentes com calcificações vasculares (28%) eram significativamente mais velhos (p=0.002), apresentavam maior prevalência de diabetes (p<0.001) e doença vascular (p=0.001), bem como níveis plasmáticos mais elevados de glicose (p<0.001) e peptídeo natriurético tipo-B (p=0.012). Após 12 meses, verificou-se progressão da calcificação em 15 dos 75 doentes reavaliados, que apresentavam, comparativamente aos seus registos iniciais, valores mais elevados de fósforo (p=0.011) e produto fosfo-cálcio (p=0.015). **Conclusões:** Na população de doentes em diálise peritoneal avaliada, a prevalência de calcificação vascular associou-se principalmente a marcadores de risco cardiovascular clássicos, como idade avançada, diabetes e níveis plasmáticos elevados de peptídeo natrurético tipo-B, enquanto que a progressão da calcificação vascular se correlacionou

significativamente com parâmetros do metabolismo fosfo-cálcio, reforçando a importância de um controlo adequado do metabolismo mineral ósseo na abordagem cardiovascular a longo prazo destes doentes.

Palavras-chave: Calcificação vascular; diálise peritoneal**;** doença cardiovascular**;** metabolismo fosfo-cálcio.

ABBREVIATIONS

ACEi	Angiotensin-converting enzyme inhibitors
APD	Automated peritoneal dialysis
ARB	Angiotensin receptor blockers
BMI	Body mass index
BNP	B-type natriuretic peptide
Ca x P	Calcium-phosphorus product
CAPD	Continuous ambulatory peritoneal dialysis
CaRB	Calcium receptor blocker
CBPBs	Calcium-based phosphate binders
CKD	Chronic kidney disease
CV	Cardiovascular
CVD	Cardiovascular disease
D/P Cr	Dialysate-to-plasma creatinine ratio
DBP	Diastolic blood pressure
ESRD	End-stage renal disease
FGF-23	Fibroblast growth factor-23
HbA1c	Glycated hemoglobin
HD	Hemodialysis
HDL	High-density lipoprotein cholesterol
HR	Heart rate
iPTH	Intact parathyroid hormone
Kt/V	Total weekly urea clearance
LDL	Low-density lipoprotein cholesterol
MGP	Matrix Gla protein
PD	Peritoneal dialysis
RRT	Renal replacement therapy
SBP	Systolic blood pressure
SHPT	Secondary hyperparathyroidism
VC	Vascular calcification
VDRA	Vitamin D receptor activator

INTRODUCTION

Chronic kidney disease (CKD) is a global public health issue, with an estimated prevalence of 8 to 16% worldwide (1). Consequently, the number of patients with end-stage renal disease (ESRD) requiring renal replacement therapy (RRT) is increasing worldwide. Peritoneal dialysis (PD), as a form of RRT, represents approximately 15% of the global population on dialysis (2).

Cardiovascular disease (CVD) is the leading cause of death in patients with ESRD on chronic dialysis, including those on PD therapy (3, 4). Indeed, the risk of cardiovascular (CV) mortality in patients on dialysis is almost nine-fold higher than in the general population (3). This extremely high CV mortality cannot be fully explained by the traditional CV risk factors frequently found in the general population, such as dyslipidemia, diabetes, hypertension and smoking (5, 6). In fact, patients with CKD have their CV risk increased by a combination of both traditional and uremia-related risk factors (3, 6).

Vascular calcification (VC) is now recognized as a significant link between CVD and CKD (7). Although VC is frequently found in the elderly, it is accelerated in CKD (8), being highly prevalent in ESRD patients, including those receiving PD therapy (4, 9). In accordance to this, the prevalence of VC is higher in patients with CKD than in the general population, and increases with advancing stages of CKD, from 40% in patients with stage 3 CKD to 80–90% in patients with stage 5 CKD on dialysis (10). These calcifications, which occur simultaneously in the intimal and medial arterial layer, are independent predictors of morbidity and mortality in ESRD patients (11-14). Intimal calcifications, common events in general population, are associated with atherosclerosis whereas medial calcifications, which are markedly increased in ESRD patients, are associated with vascular stiffness (15). The hemodynamic consequences of medial calcifications include loss of arterial elasticity, an increase in pulse wave

velocity, the development of left ventricular hypertrophy, a decrease in coronary artery perfusion and myocardial ischemia (16, 17).

Formerly, VC was seen as a passive phenomenon of calcium–phosphorus crystals precipitation from oversaturated plasma. Currently, however, it is recognized as an active process that involves vascular smooth muscle cells transformation into osteoblast-like cells (8). In fact, the pathogenesis of VC in CKD is complex**,** involving numerous factors. Some of these factors are highly prevalent in the general population, such as older age, hypertension, diabetes and dyslipidemia, whereas others are intimately related to CKD, including the abnormalities that occur in mineral metabolism (18, 19). The relative impact of each risk factor in VC incidence and progression during the course of CKD is still a matter of investigation, but the development of abnormalities in mineral metabolism probably plays a central role in VC establishment (16, 17, 19). Disturbances in mineral and bone metabolism are common in CKD given the disruption of systemic calcium and phosphorus homeostasis, with limited excretion of phosphorus and diminished hydroxylation of 25-hydroxyvitamin D to calcitriol (1,25-dihydroxyvitamin D) (17). As vitamin D deficiency and phosphorus retention progresses in CKD, the parathyroid glands become maximally stimulated, which causes secondary hyperparathyroidism (SHPT) (17). Many studies reported an association between serum calcium, phosphorus and calcium–phosphorus product and VC (7, 11, 20). Other factors related to mineral metabolism had also been associated with VC, such as vitamin D, fibroblast growth factor-23 (FGF-23), fetuin-A, matrix Gla protein (MGP) and osteoprotegerin (8, 21, 22). The role of vitamin D in the development of VC is probably complex, as reflected by the divalent results observed in clinical trials performed to evaluate the impact of the oral supplementation of this vitamin. Indeed, some authors describe an increased VC and mortality with the administration of high doses of Vitamin D (21, 23), while others suggest that lower doses may protect against VC (24).

A number of techniques are currently available to evaluate VC, including plain X-ray, ultrasonography and computed tomography (10). Although the ideal screening

test remains controversial, plain X-ray is a widely available, simple and inexpensive tool that can be used to detect and monitor VC. Additionally, it can also be useful to differentiate medial calcification from intima calcification (11): it is suggested that uniform linear calcifications (angiogram-like) are representative of medial calcification whereas irregular patchy calcifications are associated with intimal atherosclerosis (11). The simplified VC score proposed by Adragão et al. is a method based on plain radiographic films of pelvis and hands, which allows the assessment of VC and accurately predicts CV risk and mortality (25, 26).

Current therapeutic strategies for VC in ESRD population are mainly focused on the management of mineral bone disease associated with CKD, including the control of calcium and phosphorus plasmatic levels, as well as the treatment of the SHPT (4). The control of calcium and phosphorus levels is frequently achieved by the use of phosphate binders (16). The phosphate binders commonly used are sevelamer, a non-calcium containing phosphate binder, and calcium-based phosphate binders (CBPBs), including calcium carbonate and calcium acetate (16). Current data comparing sevelamer and CBPB is inconsistent (27, 28), and the effect of the phosphate binder type on VC in PD population remains unclear. Concerning SHPT therapy, the use of vitamin D receptor activator (VDRA) has been the standard treatment (16). However, they elevate calcium and phosphorus levels by increasing their intestinal absorption, as well as their mobilization from the bone (29), which can promote VC. In order to suppress the SHPT without increasing calcium and phosphrus new treatment modalities were developed, including selective VDRA and calcimimetics agents. Cinacalcet hydrochloride is a calcimimetic agent that emerges as a novel therapeutic agent for the treatment of SHPT in patients with CKD, and is efficient in both hemodialysis (HD) and PD patients, reducing calcium, phosphorus, parathyroid hormone (PTH) and FGF-23 levels (30-32). Additionally, the use of cinacalcet was associated with slower progression of VC in HD patients (33).

From what was previously exposed, we can conclude that VC is an important cardiovascular prognostic marker for patients with CKD on dialysis, which pathophysiology, assessment and management is still a matter of debate, particularly in patients on PD. Therefore, the aim of our study was to retrospectively evaluate VC in an incident PD population in order to identify factors associated with both VC prevalence and progression.

SUBJECTS AND METHODS

General Design

A retrospective, observational study was performed to investigate the impact of selected demographic, clinical, pharmacologic and PD-related factors on the prevalence and progression of VC in an incident PD population.

Subjects

The medical records of 139 incident patients at the PD Unit of Hospital de S. João from 1 January 2009 to 31 December 2011 were reviewed. All the patients without plain radiographs of pelvis and hands within the first 3 months of PD therapy were excluded (40 patients); the remaining 99 patients were included in the baseline characterization. The study population was subsequently divided in two groups according to the presence of VC at baseline and compared for demographic, clinical and biochemical variables. After 12 months, the 75 patients who remained on PD therapy were divided in two groups according to the progression of VC and compared for the aforementioned variables. The VC progression was defined as a VC score after 12 months higher than the VC score at baseline. The clinical characteristics of the 15 patients who presented VC progression were also compared, at the beginning of the study period and after 1 year of PD therapy.

Data Collection

Data collection was registry-based. Clinical information, including CV risk factors, relevant medical antecedents and usual medications were obtained from the last registry before initiation of PD. The antecedents recorded included history of diabetes, hypertension, vascular disease (defined as coronary, cerebrovascular or peripheral vascular disease) and previous RRT (HD or renal transplantation). Pharmacologic profile included angiotensin-converting enzyme inhibitors (ACEi), angiotensin receptor blockers (ARB), β-blockers, calcium receptor blockers (CaRB),

diuretics, antiplatelet agents, warfarin, statins, erythropoiesis-stimulating agents, calcium carbonate, sevelamer, VDRA and cinacalcet.

Data on anthropometric parameters, systolic blood pressure (SBP), diastolic blood pressure (DBP), heart rate (HR), PD-related factors and general biochemical profile were collected from the first registry following PD therapy initiation and after 12 months. Anthropometric parameters included weight and body mass index (BMI). The PD-related factors recorded were PD modality (automated peritoneal dialysis - APD or continuous ambulatory peritoneal dialysis – CAPD), total renal clearance, diuresis, total weekly urea clearance (Kt/V), total creatinine clearance and dialysate-to-plasma creatinine ratio (D/P Cr), obtained after a 4-hour peritoneal equilibration test performed with a hypertonic PD solution. Analytic profile included hemoglobin, albumin, alkaline phosphatase, total cholesterol, low-density lipoprotein cholesterol (LDL), high-density lipoprotein cholesterol (HDL), triglycerides, glucose, glycated hemoglobin (HbA1c), calcium, phosphorus, calcium-phosphorus product (Ca x P), C-reactive protein, pH, bicarbonate, intact parathyroid hormone (iPTH) and B-type natriuretic peptide (BNP).

Assessment of VC

VC was evaluated at baseline and after 12 months on PD therapy by plain radiographs of pelvis and hands, using the simplified score developed by Adragão et al (25). The pelvic radiographs were divided into four sections by two imaginary lines: a horizontal line over the upper limit of both femoral heads and a median vertical line over the vertebral column. The radiographs of the hands were divided, for each hand, by a horizontal line over the upper limit of the metacarpal bones. The presence of linear vascular calcifications in each section was counted as 1 and its absence as 0. The final score was the sum of all the sections, ranging from 0 to 8.

Statistical Analysis

Statistical analysis was performed using IBM® SPSS® Statistics Version 22, for Windows®. Continuous variables were expressed as mean ± standard deviation or as

median (range). Categorical variables were expressed as frequency and percentage. Comparisons between continuous variables were performed using the t-test or the Mann Whitney U test for independent samples, and t-test or Wilcoxon test for paired samples. Categorical variables were compared using the chi-square test or Fisher's exact test. *P* values < 0.05 were considered statistically significant.

RESULTS

Baseline characterization of the patients studied

Baseline characterization of the 99 patients studied is presented in Table I. The median age of this incident PD population was 45 years (range from 16 to 89 years), with 61 (62%) males and 38 (38%) females. CAPD was the predominant modality in our population and was used in 93% of the patients. All patients used standard bicarbonate based PD solutions (Physioneal, Baxter, USA) with 1.25 mmol/L of calcium. Glomerulonephritis was the most common identified cause of CKD (22%), followed by diabetes (17%) and hypertension (10%).

In this population, the prevalence of diabetes was 29% (83% type 2 and 17% type 1), 85% were hypertensive and 23% had documented vascular disease (48% had history of cardiovascular disease, 42% of cerebrovascular disease and 10% of peripheral vascular disease).

Regarding the pharmacologic profile, 90% of the patients were treated with at least one class of anti-hypertensive drugs and 76% had their anemia treated with an erythropoiesis-stimulating agent. Among the drugs that target mineral metabolism disturbances, calcium carbonate was the predominant chelating agent prescribed (36% for calcium carbonate and 24% of sevelamer use), and VDRA were more often used for the treatment of hyperparathyroidism than cinacalcet (31% *vs.* 9%). The VDRAs used were calcitriol (20% of the patients) and alphacalcidol (11% of cases). The dosage of VDRA prescribed ranged from 1.5 to 3.5 mcg per week, with a median of 1.5 mcg per week.

The prevalence of VC at baseline was 28%, with a median calcification score in these patients of 4 (range from 1 to 8).

Characterization of the population of patients with VC at baseline

The characterization of the population of patients with VC at baseline is displayed in Table II. The patients with VC at baseline, when compared with those without VC, were older (median 59 years *vs.* 42 years, p=0.002) and had a higher prevalence of both diabetes (75% *vs.* 11%, p<0.001) and vascular disease (50% *vs.* 17%, p=0.001). Patients with VC at baseline presented a higher BMI (28 ± 4 *vs.* 26 ± 4 kg/m^2, p=0.014) and a lower DBP (71 ± 16 *vs.* 81 ± 14 mmHg, p=0.004) than those without VC at baseline. No significant difference was observed in SBP or HR values between the two groups. Furthermore, no differences were found in the other demographic or clinical variables evaluated.

The treatment with β-blocker agents was more frequent in patients with VC than in those without VC (68 *vs.* 35%, p=0.003). The proportion of patients taking antiplatelet agents was also significantly higher in the group presenting VC at baseline (one antiplatelet agent: 32 *vs.* 14%, p=0.043; two antiplatelet agents: 18% *vs.* 4%, p=0.039). No differences were observed in the use of other drugs, including warfarin and drugs directed to the calcium-phosphorus metabolism, such as calcium carbonate, sevelamer, VDRA and cinacalcet.

Regarding the biochemical profile, plasmatic BNP (median 199 *vs.* 99 pg/mL, p=0.012), glucose plasmatic levels (median 138 *vs.* 87 mg/dL, p<0.001) and HbA1c (median 6.7 *vs.* 5.4%, p<0,001) were significantly higher in patients with VC at baseline. On the contrary, albumin plasmatic levels were significantly lower in this group (35.0 ± 5.3 *vs.* 38.6 ± 4.4 g/L, p=0.001). No significant differences were found in other biochemical parameters, including those related to calcium-phosphorus metabolism, such as calcium, phosphorus, calcium-phosphorus product and iPTH.

Patients with VC at baseline presented a lower peritoneal transport profile (D/P Cr: 0.7 ± 0.1 *vs.* 0.8 ± 0.1, p=0.037), and a significantly higher total creatinine clearance (188 ± 87 *vs.* 127 ± 59 L/week, p=0.004). In the group of patients with VC, a

higher renal clearance (median 8.6 *vs*. 6.1 mL/min, *p*=0.018) was also observed. No differences were documented in the remaining PD-related variables.

Characterization of the population of patients with VC progression

The characterization of the patients reevaluated after one year on PD therapy is presented in Table III. Twenty-four patients were not evaluated for VC progression: 3 patients died, 2 were transferred to HD, 8 were submitted to renal transplantation and 11 had no radiographs of pelvis and hands to assess VC progression. Therefore, 75 patients were included in the second evaluation.

Vascular calcification progression was observed in 15 patients (20%). Of these, 9 (60%) already had VC at baseline, while 6 (40%) displayed *de novo* VC (*p*=0.014). Comparatively to those without VC progression, patients that progressed were significantly older (median 63 *vs.* 46 years, *p*=0.016) and had a higher prevalence of diabetes (60 *vs.* 27%, *p*=0.014) and vascular disease (60 *vs.* 23%, *p*=0.011). Patients with VC progression presented significantly higher SBP (149 ± 30 *vs.* 132 ± 25 mmHg, *p*= 0.031) when compared to the non-progressing group. No significant differences were observed in DPB or HR values between the two groups. Additionally, no differences were found in the other demographic or clinical variables.

Pharmacologically, the proportion of patients taking ARB (60 *vs.* 23%, *p*=0.011) and β-blockers (80 *vs.* 48%, *p*=0.028) was higher in the group with VC progression. No differences in the use of other drugs were documented, including warfarin and drugs directed to the calcium-phosphorus metabolism, such as calcium carbonate, sevelamer, VDRA and cinacalcet.

Analytically, patients with VC progression had higher glucose (median 104 *vs.* 99 mg/dL, *p*=0.023) and BNP plasmatic levels (median 321 *vs.* 67 pg/mL, *p*=0.001) when compared to the non-progressing group. No differences were found in the other biochemical parameters, including plasmatic levels of calcium, phosphorus, calcium-phosphorus product and PTH.

Patients with VC progression presented a faster peritoneal transport profile (D/P Cr 0.8 ± 0.04 *vs.* 0.7 ± 0.1 mg/dL, *p*=0.006) when compared to the patients without VC progression. On the contrary, total creatinine clearance and renal clearance were similar between the two groups.

The analytic characterization of the subpopulation of PD patients that presented VC progression after 1 year on PD therapy is shown in Table IV. The biochemical profile of the 15 patients who had VC progression after 1 year, in comparison to that registered at the beginning of PD therapy, presented significantly higher phosphorus plasmatic levels (median 5.0 *vs.* 3.8 mg/dL, *p*=0.011) and higher calcium-phosphorus product (45 *vs.* 33 mg^2/dL^2, *p*=0.015). No differences were found in the other analytical parameters.

DISCUSSION

In the population of PD patients studied vascular calcification evaluated by a simplified score was frequent, being present in more than one quarter of the patients at the beginning of RRT and in 20% of the sample after one year of PD therapy. The presence of VC at baseline was mainly associated with traditional cardiovascular risk markers, such as older age, diabetes and elevated BNP plasmatic levels, whereas the progression of VC correlated also with some of the parameters of the calcium-phosphorus metabolism, namely phosphorus plasmatic levels and calcium-phosphorus product.

The prevalence of VC in our incident PD population was 28%, which was lower than that reported in the majority of the previous studies (13, 14, 19). This difference may be partly explained by the intrinsic characteristics of the population studied (age, CKD etiology or diabetes prevalence) or to the screening technique used to determine the presence of VC. Despite this, VC seems to be a frequent finding in these patients at the beginning of RRT, reflecting the importance of timely referral to pre-dialysis care in the cardiovascular risk modulation of advanced CKD patients.

In the present study, age correlated positively with both the prevalence and progression of VC, which is in line with previous evidence in this area (12, 13). Additionally, in accordance with previous studies (13, 34), both diabetes history and poorly controlled glucose levels were more frequent in patients with VC at baseline, as well as in those experiencing VC progression after one year on PD therapy. Despite the fact that glucose was previously implicated in the calcification process in bovine vascular smooth muscle cells (35), the association between diabetes and VC may also be attributed to an unfavorable lipid profile deriving from an insulin resistance state and visceral fat accumulation (13). However, in the present study, no difference was found in the lipid profile between patients with and without VC, neither the proportion of patients taking statins was significantly different between groups. One possible

explanation for these results is the fact that we have assessed medial calcification, and the lipid profile appears to be predominantly associated with atherosclerosis and intimal calcification. Moreover, fasting plasma glucose seems to be a better independent determinant of the progression of VC than the other metabolic syndrome risk factors (36).

In our PD population BNP plasmatic levels were significantly higher in patients with VC at baseline, as well as in those who experienced VC progression over 1 year on PD therapy. Fluid overload, frequent in ESRD patients, stimulates the secretion of BNP by the myocardium. The role of BNP on the VC process in PD population remains unclear, but it is known that serum BNP levels are more than 10-fold higher in patients on PD than in the general population, and are associated with CV mortality (37). Additionally, BNP circulating levels in these patients may also be related to the presence of heart failure or the degree of residual renal function, as previously suggested (37). Despite the possible interference of all these factors, the association between VC and BNP circulating levels that we have observed probably reflects the overall cardiovascular risk profile of this dialysis population and may assist in the early detection of a subgroup of patients more disposed to VC development.

In our patients, the use of β-blockers was positively correlated to the presence of VC at baseline and to the progression of VC. In fact, β-blockers may promote VC through sympathetic activity modulation, influencing the trophic effects of this system on the peripheral vasculature (38). However, it should be noted that β-blockers are frequently prescribed to patients with higher cardiovascular risk, which might constitute by itself a confounding factor for the association of these agents to VC. Even so, we can speculate if the different cardio-modulating pharmacological agents frequently used in PD patients may have a distinct impact in the risk of VC progression and, for that reason, be preferred over the other therapeutic possibilities in patients more prone to VC development.

The present study did not found any difference regarding the treatment with warfarin in PD patients, whereas treatment with antiplatelet agents was positively associated with VC. It is known that warfarin impairs the synthesis and function of the MGP, a vitamin K–dependent protein that is a potent inhibitor of tissue calcification (39). The absence of a statistically significant association between warfarin therapy and VC may be explained by the limited proportion of patients taking warfarin in our population. The role of antiplatelet agents for cardiovascular disease management in ESRD remains unclear (40), but they are frequently prescribed to patients with an elevated CV risk profile and with a higher prevalence of disrupted vascular function.

In this study, we have not identified a significant association between C-reactive protein plasmatic levels and the progression of VC. Inflammation is a recognized stimulus for vascular calcification and C-reactive protein has been associated with progression of VC in HD patients (41). Our findings are in accordance with previous observations (13) and may be explained by the fact that PD patients, for reasons mainly related to the intrinsic characteristics of the dialysis modality, may be less exposed to immunogenic materials and, as a consequence, less inflamed. A study directed to evaluate the relation between different inflammatory markers and VC in patients treated with HD or PD would be, naturally, very informative.

In our population no difference was found in the calcium and phosphorus metabolism between patients with and without VC at baseline. However, it is noteworthy that a higher phosphorus plasmatic levels and calcium-phosphorus product was observed after 1 year of PD therapy in the group of patients who presented VC progression. Despite the relative importance attributed by different authors to the factors previously mentioned, the calcium-phosphorus metabolism has been profoundly implicated in VC process. In fact, VC was previously associated with the degree of calcium and phosphorus control, the suppression of PTH, and the use of CBPBs (18). In this study, no difference was found regarding the type of P-binder used. Although some studies reported that treatment with sevelamer had a significant role in the

attenuation of the VC progression when compared to CBPBs (27), others did not found significant differences between these two forms of therapy (28), particularly during the first year on dialysis (42). An explanation proposed for the protective effect of sevelamer was the influence in lipid profile, decreasing LDL levels (16). In vitro studies have shown that LDL promotes vascular smooth muscle cells calcification, whereas HDL inhibits it (43). Thus, the improvement in lipid profile might play a role in the lower degree of VC observed after sevelamer therapy. This theory was corroborated in a study in HD patients, who reported similar VC progression rates between a group treated with calcium acetate plus intensive lowering of LDL levels with atorvastatin and other treated with sevelamer alone (28). Our population presented a controlled lipid profile and the LDL plasmatic levels were below the value associated with increased CV risk, probably explaining the absence of correlation between sevelamer therapy and VC prevalence and progression.

In the present study no association was found between VDRA use and VC. It is known that use of VDRA results in the elevation of calcium and phosphorus plasmatic levels by increasing their intestinal absorption, as well as by their mobilization from the bone (29). In our PD population mainly non-selective VDRA were used. Even though non-selective and selective VDRA are both effective in inducing suppression of PTH secretion, selective VDRA may cause less hypercalcaemia and hyperphosphataemia due to their cellular selectivity (44), and have been reported to grant a survival advantage over non-selective VDRA (45). The absence of correlation between Vitamin D supplementation and VC progression in our study may be explained by the predominant use of non-selective VDRA agents, counteracting the possible survival advantage of VDRA therapy in the calcification process. More trials will be required to clarify the role of VDRA in VC development, as well as to determine the influence of the different types of VDRA in VC progression in the PD population.

Concerning the treatment with cinacalcet, an agent recently developed for SHPT management without increasing calcium and phosphorus, no difference was

found in our study between patients with and without VC at baseline and after 1 year of PD therapy. Previous studies have documented an association between cinacalcet therapy and a slower progression of VC, when compared to flexible doses of vitamin D alone (33). Additionally, it was reported a case of regression of VC in a patient treated with cinacalcet (46). In the present study, the limited use of cinacalcet in our population may have contributed to the absence of significant differences observed. Nevertheless, data regarding the impact of cinacalcet therapy in VC is still very limited and more trials will be necessary to confirm the role of this therapeutic agent in VC modulation.

With respect to PD-related variables, patients with VC progression revealed a faster peritoneal transport profile when compared to patients without VC progression, whereas patients with VC at baseline presented a slower peritoneal transport than those without VC. Actually, several studies have linked fast peritoneal transport with higher mortality in PD (47), but its relation with VC is not well established. The patients with VC at baseline presented also a higher total renal clearance. These results appears to be contradictory, since VC is positively related to mortality (11-14) and the residual renal function is inversely correlated with mortality on PD patients (48). One possible explanation may rely on the fact that, as previously observed in other studies, the rate of decline of residual renal function may be more powerful in predicting all-cause mortality in the PD population than baseline residual renal function (49). Other possible explanation may be related to a more precocious referral to RRT of patients with a higher CV disease burden that may also present, at baseline, a higher risk for VC development.

Finally, in concordance with previous studies, VC progression was more frequent in patients who presented VC at baseline (12, 13). In fact, patients without visible calcification often do not experience VC progression or only have minimal VC over the time on dialysis (42). These findings raise the possibility that some patients may be “protected” against VC and express a lighter form of vascular disease even in the presence of advanced CKD. The identification of factors possibly associated to this

protective profile is imperative, as it may contribute to the development of new therapeutic strategies oriented to limit VC development in dialysis patients.

We recognize important limitations of this study, mainly inherent to its retrospective and single-center nature, which can be a source of bias. On the other hand, the number of patients evaluated is the main strength of our work, since previous studies in PD patients presented, generally, limited samples.

In conclusion, in our population of PD patients VC was a common finding at the beginning of RRT and was associated with some of the classical CV risk markers, such as older age, diabetes and elevated BNP levels. Vascular calcification progression after 1 year on PD therapy was mainly observed in patients with VC at baseline and less frequent in patients without VC in the first assessment. Despite the known impact of the calcium-phosphorus metabolism on VC development, we have documented a positive correlation between phosphorus plasmatic levels and calcium-phosphorus product and VC only in the subpopulation of PD patients that presented VC progression after 1 year on PD therapy, reinforcing the importance of an adequate SHPT control in the long term management of the cardiovascular risk of these patients.

ACKNOWLEDGMENTS

The authors thank to the Department of Health Information and Decision Sciences from Faculty of Medicine of University of Porto, for the assistance in the statistical analysis.

REFERENCES

1. Jha V, Garcia-Garcia G, Iseki K, Li Z, Naicker S, Plattner B, et al. Chronic kidney disease: global dimension and perspectives. Lancet. 2013;382(9888):260-72.

2. Gokal R. Peritoneal dialysis in the 21st century: an analysis of current problems and future developments. J Am Soc Nephrol. 2002;13 Suppl 1:S104-16.

3. Krediet RT, Balafa O. Cardiovascular risk in the peritoneal dialysis patient. Nat Rev Nephrol. 2010;6(8):451-60.

4. Wang AY. Vascular and valvular calcification in chronic peritoneal dialysis patients. Int J Nephrol. 2011;2011:198045.

5. Zoccali C. Cardiovascular risk in uraemic patients-is it fully explained by classical risk factors? Nephrol Dial Transplant. 2000;15(4):454-7.

6. Garcia-Lopez E, Carrero JJ, Suliman ME, Lindholm B, Stenvinkel P. Risk factors for cardiovascular disease in patients undergoing peritoneal dialysis. Perit Dial Int. 2007;27 Suppl 2:S205-9.

7. Raggi P, Boulay A, Chasan-Taber S, Amin N, Dillon M, Burke SK, et al. Cardiac calcification in adult hemodialysis patients. A link between end-stage renal disease and cardiovascular disease? J Am Coll Cardiol. 2002;39(4):695-701.

8. Moe SM, Chen NX. Mechanisms of vascular calcification in chronic kidney disease. J Am Soc Nephrol. 2008;19(2):213-6.

9. Ammirati AL, Moysés RMA, Canziani ME. Vascular calcification in peritoneal dialysis patients. Peritoneal Dialysis International. 2008;28(Supplement 2):S20-S5.

10. Karohl C, Gascon LD, Raggi P. Noninvasive imaging for assessment of calcification in chronic kidney disease. Nat Rev Nephrol. 2011;7(10):567-77.

11. London GM, Guerin AP, Marchais SJ, Metivier F, Pannier B, Adda H. Arterial media calcification in end-stage renal disease: impact on all-cause and cardiovascular mortality. Nephrol Dial Transplant. 2003;18(9):1731-40.

12. Lee MJ, Shin DH, Kim SJ, Oh HJ, Yoo DE, Ko KI, et al. Progression of aortic arch calcification over 1 year is an independent predictor of mortality in incident peritoneal dialysis patients. PLoS One. 2012;7(11):e48793.

13. Ammirati AL, Dalboni MA, Cendoroglo M, Draibe SA, Santos RD, Miname M, et al. The progression and impact of vascular calcification in peritoneal dialysis patients. Perit Dial Int. 2007;27(3):340-6.

14. Noordzij M, Cranenburg EM, Engelsman LF, Hermans MM, Boeschoten EW, Brandenburg VM, et al. Progression of aortic calcification is associated with disorders of mineral metabolism and mortality in chronic dialysis patients. Nephrol Dial Transplant. 2011;26(5):1662-9.

15. Toussaint ND, Kerr PG. Vascular calcification and arterial stiffness in chronic kidney disease: implications and management. Nephrology (Carlton). 2007;12(5):500-9.

16. Nitta K. Vascular calcification in patients with chronic kidney disease. Ther Apher Dial. 2011;15(6):513-21.

17. Eddington H, Kalra PA. The association of chronic kidney disease-mineral bone disorder and cardiovascular risk. J Ren Care. 2010;36 Suppl 1:61-7.

18. Cannata-Andia JB, Rodriguez-Garcia M, Carrillo-Lopez N, Naves-Diaz M, Diaz-Lopez B. Vascular calcifications: pathogenesis, management, and impact on clinical outcomes. J Am Soc Nephrol. 2006;17(12 Suppl 3):S267-73.

19. Kim HG, Song SW, Kim TY, Kim YO. Risk factors for progression of aortic arch calcification in patients on maintenance hemodialysis and peritoneal dialysis. Hemodial Int. 2011;15(4):460-7.

20. Speer MY, Yang HY, Brabb T, Leaf E, Look A, Lin WL, et al. Smooth muscle cells give rise to osteochondrogenic precursors and chondrocytes in calcifying arteries. Circ Res. 2009;104(6):733-41.

21. Jono S, Nishizawa Y, Shioi A, Morii H. 1,25-Dihydroxyvitamin D3 increases in vitro vascular calcification by modulating secretion of endogenous parathyroid hormone-related peptide. Circulation. 1998;98(13):1302-6.

22. Nasrallah MM, El-Shehaby AR, Salem MM, Osman NA, El Sheikh E, Sharaf El Din UA. Fibroblast growth factor-23 (FGF-23) is independently correlated to aortic calcification in haemodialysis patients. Nephrol Dial Transplant. 2010;25(8):2679-85.

23. Henley C, Colloton M, Cattley RC, Shatzen E, Towler DA, Lacey D, et al. 1,25-Dihydroxyvitamin D3 but not cinacalcet HCl (Sensipar/Mimpara) treatment mediates aortic calcification in a rat model of secondary hyperparathyroidism. Nephrol Dial Transplant. 2005;20(7):1370-7.

24. Mathew S, Lund RJ, Chaudhary LR, Geurs T, Hruska KA. Vitamin D receptor activators can protect against vascular calcification. J Am Soc Nephrol. 2008;19(8):1509-19.

25. Adragao T, Pires A, Lucas C, Birne R, Magalhaes L, Goncalves M, et al. A simple vascular calcification score predicts cardiovascular risk in haemodialysis patients. Nephrol Dial Transplant. 2004;19(6):1480-8.

26. Adragao T, Pires A, Birne R, Curto JD, Lucas C, Goncalves M, et al. A plain X-ray vascular calcification score is associated with arterial stiffness and mortality in dialysis patients. Nephrol Dial Transplant. 2009;24(3):997-1002.

27. Chertow GM, Burke SK, Raggi P. Sevelamer attenuates the progression of coronary and aortic calcification in hemodialysis patients. Kidney Int. 2002;62(1):245-52.

28. Qunibi W, Moustafa M, Muenz LR, He DY, Kessler PD, Diaz-Buxo JA, et al. A 1-year randomized trial of calcium acetate versus sevelamer on progression of coronary artery calcification in hemodialysis patients with comparable lipid control: the Calcium Acetate Renagel Evaluation-2 (CARE-2) study. Am J Kidney Dis. 2008;51(6):952-65.

29. Drueke TB, Massy ZA. Role of vitamin D in vascular calcification: bad guy or good guy? Nephrol Dial Transplant. 2012;27(5):1704-7.

30. Lindberg JS, Culleton B, Wong G, Borah MF, Clark RV, Shapiro WB, et al. Cinacalcet HCl, an oral calcimimetic agent for the treatment of secondary hyperparathyroidism in hemodialysis and peritoneal dialysis: a randomized, double-blind, multicenter study. J Am Soc Nephrol. 2005;16(3):800-7.

31. Kim HJ, Kim H, Shin N, Na KY, Kim YL, Kim D, et al. Cinacalcet lowering of serum fibroblast growth factor-23 concentration may be independent from serum Ca, P, PTH and dose of active vitamin D in peritoneal dialysis patients: a randomized controlled study. BMC Nephrol. 2013;14:112.

32. Portoles J, Lopez-Sanchez P, Bajo MA, Castellano I, del Peso G, Rodriguez JR, et al. Cinacalcet improves control of secondary hyperparathyroidism in peritoneal dialysis: a multicenter study. Perit Dial Int. 2012;32(2):208-11.

33. Raggi P, Chertow GM, Torres PU, Csiky B, Naso A, Nossuli K, et al. The ADVANCE study: a randomized study to evaluate the effects of cinacalcet plus low-dose vitamin D on vascular calcification in patients on hemodialysis. Nephrol Dial Transplant. 2011;26(4):1327-39.

34. Janda K, Krzanowski M, Gajda M, Dumnicka P, Fedak D, Lis GJ, et al. Impaired fasting glucose and diabetes as predictors for radial artery calcification in end stage renal disease patients. Int J Endocrinol. 2013;2013:969038.

35. Chen NX, Duan D, O'Neill KD, Moe SM. High glucose increases the expression of Cbfa1 and BMP-2 and enhances the calcification of vascular smooth muscle cells. Nephrol Dial Transplant. 2006;21(12):3435-42.

36. Kramer CK, von Muhlen D, Gross JL, Laughlin GA, Barrett-Connor E. Blood pressure and fasting plasma glucose rather than metabolic syndrome predict coronary artery calcium progression: the Rancho Bernardo Study. Diabetes Care. 2009;32(1):141-6.

37. Wang AY, Lam CW, Yu CM, Wang M, Chan IH, Zhang Y, et al. N-terminal pro-brain natriuretic peptide: an independent risk predictor of cardiovascular congestion, mortality, and adverse cardiovascular outcomes in chronic peritoneal dialysis patients. J Am Soc Nephrol. 2007;18(1):321-30.

38. Pierroz DD, Bouxsein ML, Rizzoli R, Ferrari SL. Combined treatment with a beta-blocker and intermittent PTH improves bone mass and microarchitecture in ovariectomized mice. Bone. 2006;39(2):260-7.

39. Palaniswamy C, Sekhri A, Aronow WS, Kalra A, Peterson SJ. Association of warfarin use with valvular and vascular calcification: a review. Clin Cardiol. 2011;34(2):74-81.

40. Harmon JP, Zimmerman DL, Zimmerman DL. Anticoagulant and antiplatelet therapy in patients with chronic kidney disease: risks versus benefits review. Curr Opin Nephrol Hypertens. 2013;22(6):624-8.

41. Jung HH, Kim SW, Han H. Inflammation, mineral metabolism and progressive coronary artery calcification in patients on haemodialysis. Nephrol Dial Transplant. 2006;21(7):1915-20.

42. Block GA, Spiegel DM, Ehrlich J, Mehta R, Lindbergh J, Dreisbach A, et al. Effects of sevelamer and calcium on coronary artery calcification in patients new to hemodialysis. Kidney Int. 2005;68(4):1815-24.

43. Proudfoot D, Davies JD, Skepper JN, Weissberg PL, Shanahan CM. Acetylated low-density lipoprotein stimulates human vascular smooth muscle cell calcification by promoting osteoblastic differentiation and inhibiting phagocytosis. Circulation. 2002;106(24):3044-50.

44. Sprague SM, Llach F, Amdahl M, Taccetta C, Batlle D. Paricalcitol versus calcitriol in the treatment of secondary hyperparathyroidism. Kidney Int. 2003;63(4):1483-90.

45. Teng M, Wolf M, Lowrie E, Ofsthun N, Lazarus JM, Thadhani R. Survival of patients undergoing hemodialysis with paricalcitol or calcitriol therapy. N Engl J Med. 2003;349(5):446-56.

46. Salgueira M, Martinez Al, Milan JA. Regression of vascular calcification in a patient treated with cinacalcet: a case report. Nefrologia. 2011;31(5):602-6.

47. Brimble KS, Walker M, Margetts PJ, Kundhal KK, Rabbat CG. Meta-analysis: peritoneal membrane transport, mortality, and technique failure in peritoneal dialysis. J Am Soc Nephrol. 2006;17(9):2591-8.

48. Perl J, Bargman JM. The importance of residual kidney function for patients on dialysis: a critical review. Am J Kidney Dis. 2009;53(6):1068-81.

49. Liao CT, Chen YM, Shiao CC, Hu FC, Huang JW, Kao TW, et al. Rate of decline of residual renal function is associated with all-cause mortality and technique failure in patients on long-term peritoneal dialysis. Nephrol Dial Transplant. 2009;24(9):2909-14.

TABLES

TABLE I

Baseline characterization of the patients studied (*n*=99)

Age (years)	45 (16-89)
Male gender	61 (62%)
Diabetes	29 (29%)
Hypertension	84 (85%)
Smoking	20 (20%)
Vascular Disease	23 (23%)
Cardiovascular Disease	14 (14%)
Cerebrovascular Disease	12 (12%)
Peripheral Vascular Disease	3 (3%)
CKD Etiology	
Diabetes	17 (17%)
Hypertension	10 (10%)
Glomerulonephritis	22 (22%)
Polycystic kidney disease	8 (8%)
Undetermined	25 (26%)
Other	17 (17%)
Previous HD therapy	21 (21%)
Previous renal transplantation	6 (6%)
Weight (Kg)	71 ± 14
BMI (kg/m^2)	26 ± 4
SBP (mmHg)	139 ± 23
DBP (mmHg)	78 ± 15
HR	76 ± 13
Pharmacologic profile	

ACEi	44 (44%)
ARB	25 (25%)
β-blocker	44 (44%)
CaRB	53 (54%)
Diuretic	72 (73%)
One antiplatelet agent	19 (19%)
Two antiplatelet agents	8 (8%)
Warfarin	4 (4%)
Statin	53 (54%)
Calcium carbonate	36 (36%)
Sevelamer	24 (24%)
Vitamin D receptor activator	31 (31%)
Calcitriol	20 (20%)
Alphacalcidol	11 (11%)
Dosage/week (mcg)	1,5 (0,5-3,5)
Erythropoiesis-stimulating agent	75 (76%)
Cinacalcet	9 (9%)
Biochemical profile	
Hemoglobin (g/dL)	11,7 ± 1,5
Albumin (g/L)	37,6 ± 4,9
Alkaline Phosphatase (U/L)	90 (10-310)
Total Cholesterol (mg/dL)	191 ± 50
HDL (mg/dL)	46 (13-204)
LDL (mg/dL)	102 ± 44
Triglycerides (mg/dL)	143 (55-565)
Glucose (mg/dL)	92 (57-308)
HbA1c (%)	5,7 (3,9-11,3)
Calcium (mg/dL)	9,2 (7,2-11,0)
Phosphorus (mg/dL)	4,2 (1,2-12,2)

Ca x P (mg^2/dL^2)	39 (11-98)
C-reactive protein (mg/L)	4,0 (0,2-84,8)
pH	7,3 (7,1-7,5)
Bicarbonate (mmol/L)	28,4 (13,9-62,5)
iPTH (pg/mL)	316 (41-1578)
BNP (pg/mL)	127 (11-2308)
PD-related variables	
PD modality	
CAPD	92 (93%)
APD	7 (7%)
Total Renal Clearance (mL/min)	7,2 (0-38,0)
Diuresis (mL)	1500 (0-4600)
Kt/V	2,3 (0,8-8,4)
Total Clearance (L/week)	144 ± 72
D/P Cr (mg/dL)	0,75 ± 0,10
Vascular Calcification	28 (28%)

Results are expressed in: frequency (percentage); median (range); mean (standard deviation).

.

TABLE II

Characterization of the Patients Without and With VC at Baseline

	Without VC (*n*=71)	With VC (*n*=28)	*p* Value
Age	42 (16-89)	59 (25-80)	**0,002**[a]
Gender Male	42 (59%)	19 (68%)	0,423[b]
Diabetes	8 (11%)	21 (75%)	**<0,001**[b]
Hypertension	58 (82%)	26 (93%)	0,221[c]
Smoking	15 (21%)	5 (18%)	0,698[b]
Vascular Disease	12 (17%)	14 (50%)	**0,001**[b]
CKD			
Previous HD therapy	15 (21%)	6 (21%)	0,974[b]
Previous renal transplantation	2 (3%)	4 (14%)	0,052[c]
Weight (kg)	69 ± 14	76 ± 11	**0,021**[d]
BMI (kg/m^2)	26 ± 4	28 ± 4	**0,014**[d]
SBP (mmHg)	138 ± 20	141 ± 27	0,580[d]
DPB (mmHg)	81 ± 14	71 ± 16	**0,004**[d]
HR	76 ± 12	72 ± 15	0,157[d]
Pharmacological profile			
ACEi	34 (48%)	10 (36%)	0,272[b]
ARB	16 (22%)	9 (32%)	0,322[b]
β-blocker	25 (35%)	19 (68%)	**0,003**[b]
CaRB	34 (48%)	19 (68%)	0,073[b]
Diuretic	49 (69%)	23 (82%)	0,149[b]
One antiplatelet agent	10 (14%)	9 (32%)	**0,043**[b]
Two antiplatelet agents	3 (4%)	5 (18%)	**0,039**[c]
Warfarin	2 (3%)	2 (7%)	0,317[c]
Statin	35 (49%)	18 (64%)	0,178[b]
Calcium carbonate	23 (32%)	13 (46%)	0,191[b]
Sevelamer	20 (28%)	4 (14%)	0,147[b]

Vitamin D receptor activator	25 (35%)	6 (21%)	0,183[b]
Calcitriol	16 (64%)	4 (67%)	1,000[c]
Alphacalcidol	9 (36%)	2 (33%)	
Dosage/week (mcg)	1,5 (0,5-3,5)	1,5 (0,75-3,0)	0,770[a]
Erythropoiesis-stimulating agent	52 (73%)	23 (82%)	0,352[b]
Cinacalcet	7 (10%)	2 (7%)	1,000[c]
Biochemical profile			
Hemoglobin (g/dL)	11,6 ± 1,5	12,0 ± 1,5	0,257[d]
Albumin (g/L)	38,6 ± 4,4	35,0 ± 5,3	**0,001**[d]
Alkaline Phosphatase (U/L)	87 (10-310)	110 (42-258)	0,062[a]
Total Cholesterol (mg/dL)	193 ± 51	185 ± 49	0,431[d]
HDL (mg/dL)	49 (13-204)	44 (24-147)	0,192[a]
LDL (mg/dL)	102 ± 45	103 ± 43	0,932[d]
Triglycerides (mg/dL)	145 (55-565)	135 (69-494)	0,747[a]
Glucose (mg/dL)	87 (57-167)	138 (67-308)	**<0,001**[a]
HbA1c (%)	5,4 (3,9-11,3)	6,7 (5,4-10,9)	**<0,001**[a]
Calcium (mg/dL)	9,2 (7,2-11,0)	9,2 (7,2-10,4)	0,731[a]
Phosphorus (mg/dL)	4,3 (2,3-9,4)	4,1 (1,2-12,2)	0,228[a]
Ca x P (mg^2/dL^2)	38,7 (21,3-84,6)	34,9 (10,5-97,6)	0,208[a]
C-reactive protein (mg/L)	3,7 (0,2-84,8)	5,4 (0,8-38,8)	0,797[a]
pH	7,3 (7,1-7,5)	7,3 (7,2-7,4)	0,091[a]
Bicarbonate (mmol/L)	28,0 (13,9-62,5)	29,0 (17,0-35,2)	0,220[a]
iPTH (pg/mL)	316 (41-1578)	298 (91-957)	0,870[a]
BNP (pg/mL)	99 (11-2076)	199 (25-2308)	**0,012**[a]
PD-related variables			
PD modality			
CAPD	65 (92%)	27 (96%)	0,669[c]
APD	6 (8%)	1 (4%)	
Total renal clearance (mL/min)	6,1 (0-19,4)	8,6 (0-38,0)	**0,018**[a]

Diuresis (mL)	1500 (0-4600)	1600 (0-3000)	0,725[a]
Kt/V	2,2 (0,8-4,9)	2,4 (1,5-8,4)	0,389[a]
Total clearance (L/week)	127 ± 59	188 ± 87	**0,004**[d]
D/P Cr (mg/dL)	0,8 ± 0,1	0,7 ± 0,1	**0,037**[d]

Results are expressed in: frequency (percentage); median (range); mean (standard deviation).

[a] Mann-Whitney U; [b] Chi-square; [c] Fisher's exact test; [d] t-test.

TABLE III

Characterization of the Patients Without and With VC Progression

	Without VC progression (n=60)	With VC progression (n=15)	*p* Value
Age	46 (17-90)	63 (37-76)	**0,016**[a]
Gender Male	36 (60%)	10 (67%)	0,635[b]
Diabetes	16 (27%)	9 (60%)	**0,014**[b]
Hypertension	47 (78%)	15 (100%)	0,059[c]
Smoking	10 (17%)	3 (20%)	0,412[c]
Vascular Disease	14 (23%)	9 (60%)	**0,011**[c]
CKD			
Previous HD therapy	7 (12%)	4 (27%)	0,215[c]
Previous renal transplantation	3 (5%)	2 (13%)	0,260[c]
Weight (kg)	71 ± 14	73 ± 13	0,593[d]
BMI (kg/m^2)	27 ± 4	27 ± 4	0,769[d]
SBP (mmHg)	132 ± 25	149 ± 30	**0,031**[d]
DPB (mmHg)	76 ± 14	76 ± 14	0,935[d]
HR	76 ± 14	76 ± 15	0,875[d]
Pharmacologic profile			
ACEi	38 (63%)	8 (53%)	0,477[b]
ARB	14 (23%)	9 (60%)	**0,011**[c]
β-blocker	29 (48%)	12 (80%)	**0,028**[b]
CaRB	30 (50%)	10 (67%)	0,247[b]
Diuretic	44 (73%)	14 (93%)	0,057[c]
One antiplatelet agent	11 (18%)	5 (33%)	0,289[c]
Two antiplatelet agents	5 (8%)	2 (13%)	0,622[c]
Warfarin	3 (5%)	1 (7%)	1,000[c]
Statin	44 (73%)	13 (87%)	0,499[c]
Calcium carbonate	14 (23%)	7 (47%)	0,106[c]
Sevelamer	28 (47%)	6 (40%)	0,643[b]

Vitamin D receptor activator	38 (63%)	7 (47%)	0,239[b]
Calcitriol	9 (24%)	2 (29%)	1,000[c]
Alphacalcidol	29 (76%)	5 (71%)	
Dosage/week (mcg)	1,0 (0,5-3,5)	1,0 (0,75-3,5)	0,691[a]
Erythropoiesis-stimulating agent	41 (68%)	13 (86%)	0,496[c]
Cinacalcet	21 (35%)	5 (33%)	0,903[b]
Biochemical profile			
Hemoglobin (g/dL)	11,5 ± 1,7	10,9 ± 1,8	0,190[d]
Albumin (g/L)	38,2 ± 3,9	36,1 ± 4,6	0,075[d]
Alkaline Phosphatase (U/L)	107 (48-402)	105 (35-328)	0,882[a]
Total Cholesterol (mg/dL)	180 ± 37	163 ± 37	0,107[d]
HDL (mg/dL)	47 (28-91)	43 (29-67)	0,589[a]
LDL (mg/dL)	103 ± 29	88 ± 35	0,097[d]
Triglycerides (mg/dL)	136 (66-841)	128 (50-264)	0,804[a]
Glucose (mg/dL)	89 (50-380)	104 (76-190)	**0,023**[a]
HbA1c (%)	5,7 (4,6-8,9)	6,0 (5,0-11,8)	0,054[a]
Calcium (mg/dL)	9,0 (7,2-18,8)	9,0 (7,6-10,6)	0,433[a]
Phosphorus (mg/dL)	4,6 (3,2-7,8)	5,0 (3,2-6,3)	0,605[a]
Ca x P (mg^2/dL^2)	41 (28-132)	45 (29-53)	0,676[a]
C-reactive protein (mg/L)	2,3 (0,3-30,3)	3,9 (0,5-105,4)	0,114[a]
pH	7,3 (7,2-7,5)	7,3 (7,2-7,4)	0,721[a]
Bicarbonate (mmol/L)	28,9 (18,6-36,5)	28,8 (31,2-41,7)	0,545[a]
iPTH (pg/mL)	409 (129-1441)	408 (38-1245)	0,968[a]
BNP (pg/mL)	67 (11-1350)	321 (23-19154)	**0,001**[a]
PD-related variables			
PD modality			
CAPD	53 (88%)	12 (80%)	0,408[c]
APD	7 (12%)	3 (20%)	
Total renal clearance (mL/min)	5,7 (0-17,84)	7,2 (0-17,5)	0,936[a]

Diuresis (mL)	1500 (0-2850)	1250 (0-2600)	0,236[a]
Kt/V	2,0 (0,9-4,5)	2,3 (1,2-4,3)	0,438[a]
Total clearance (L/week)	123 ± 62	130 ± 77	0,674[d]
D/P Cr (mg/dL)	0,7 ± 0,1	0,8 ± 0,04	**0,006**[d]

Results are expressed in: frequency (percentage); median (range); mean (standard deviation).

[a] Mann-Whitney U; [b] Chi-square; [c] Fisher's exact test; [d] t-test.

TABLE IV

Biochemical Profile of the Patients With VC Progression

	Baseline (n=15)	After 1 Year (n=15)	*p* Value
Hemoglobin (g/dL)	11,7 ± 1,6	10,9 ± 1,3	0,146[a]
Albumin (g/L)	36,3 ± 3,8	36,1 ± 4,5	0,879[a]
Alkaline Phosphatase (U/L)	112 (40-237)	109 (34-328)	0,551[b]
Total Cholesterol (mg/dL)	169 ± 41	163 ± 37	0,497[a]
HDL (mg/dL)	44 ± 12	45 ± 11	0,618[a]
LDL (mg/dL)	95 ± 34	88 ± 35	0,453[a]
Triglycerides (mg/dL)	124 (69-494)	128 (50-264)	0,670[b]
Glucose (mg/dL)	98 (78-279)	104 (76-190)	0,113[b]
HbA1C (%)	6,2 (5,4-10,9)	6,0 (5,0-11,8)	0,753[b]
Calcium (mg/dL)	8,9 ± 0,8	8,8 ± 0,8	0,626[a]
Phosphorus (mg/dL)	3,8 (1,2-12,2)	5,0 (3,2-6,3)	**0,011**[b]
Ca x P (mg^2/dL^2)	33,3 (10,5-97,6)	45,0 (29,4-53,0)	**0,015**[b]
C-reactive protein (mg/L)	6,3 (0,8-38,8)	3,5 (0,5-55,9)	0,114[a]
pH	7,3 ± 0,05	7,3 ± 0,06	0,594[b]
Bicarbonate (mmol/L)	28,9 (18,6-36,5)	28,8 (31,2-41,7)	0,281[b]
iPTH (pg/mL)	347 (90-1321)	408 (38-1545)	0,233[b]
BNP (pg/mL)	203 (60-2308)	321 (23-19154)	0,061[b]

Results are expressed in: median (range); mean (standard deviation);

[a] t-test for pared groups; [b] Wilcoxon.

Conflicts of interest

The authors declare that there are no conflicts of interest.

AGRADECIMENTOS

Gostaria de agradecer à orientadora desta dissertação, a Mestre Carla Alexandra Ribeiro dos Santos Araújo, bem como ao Serviço de Nefrologia do Hospital de S. João, pela disponibilidade com que acolheram este projeto. Gostaria ainda de deixar uma palavra de agradecimento à minha colega, Doutora Joana Barbosa Henriques e Queiroz Machado, que me acompanhou ao longo do desenvolvimento desde trabalho.

NORMAS DA REVISTA

Portuguese Journal of Nephrology & Hypertension

Portuguese Journal of
Nephrology & Hypertension
ISSN 2183-1289
Revista indexada no SciELO Citation Index da Thomson Reuters
The journal is indexed in Thompson Reuter's SciELO Citation Index

INSTRUCTIONS TO AUTHORS

AIMS AND SCOPE

Portuguese Journal of Nephrology and Hypertension is the official organ of the Portuguese Society of Nephrology and is published quarterly. Supplementary issues on selected themes may also be published at the discretion of the Editor-in-Chief.

The Journal publishes articles on clinical or laboratory topics of relevance to nephrology, dialysis, transplantation and hypertension. Papers relating to basic immunology, physiology, genetics and epidemiology are accepted when kidney related.

Portuguese Journal of Nephrology and Hypertension publishes Editorials and in depth Reviews (by invitation only), Original Articles, Short Communications, Technical Notes, Case Reports and Letters. Articles are accepted and published in English. Manuscripts submitted to the *Portuguese Journal of Nephrology and Hypertension* will be sent for peer review on the understan ding that the author(s) have not published the material elsewhere.

Portuguese Journal of Nephrology and Hypertension complies with the Uniform Requirements for Manuscripts Submitted to Biomedical Journals produced by the ICMJE (International Com mittee of Medical Journal Editors). Please see http://www.icmje.org

REVIEW AND PUBLICATION SPEED

All submissions will be subject to an immediate editorial screening process by the Editor-in-Chief after which they will normally be sent to three reviewers. The Editor-in-Chief will make every effort to reach a decision on all submitted papers within 8 weeks of receipt. Papers will normally be published in the next issue to go to press after their acceptance. Papers that do not meet the scientific standards of the journal may be declined by the Editor-in-Chief without further review.

MANUSCRIPT INSTRUCTIONS

The typed manuscript should be submitted to the Editor-in-Chief by electronic mail at the following address: r.alvesrpnh@spnefro.pt.

The text should be double spaced. Manuscripts should bear the name, address and e-mail of the corresponding author. Should the manuscript be accepted for publication the authors will be asked to give signed consent for publication in a letter which must contain the statement that “the results presented in this paper have not been published previously in whole or in part except in abstract form”.

Title Page: The title page should carry the full title of the paper and the first name, middle initial (if applicable) and last name of each author, plus the name and address of the institution(s) at which the work was done; in the case of different institutions the author(s) should be identified using numbers. In the case of Portuguese language authors the title must also be translated into Portuguese.

Abstract: Not more than 300 words. Do not use abbreviations. In the case of Portuguese language authors the abstract must also be translated into Portuguese.

Key-Words: not more than 6, in alphabetical order, and the terms used (when possible) should be from the Medical Subject Headings list of the *Index Medicus*. In the

case of Portuguese language authors the key-words must also be translated into Portuguese.

Text: The order of the text should be as follows: Introduction, Subjects and Methods (any statistical method must be detailed in this section), Results, Discussion, Acknowledgments, References (see below), Tables, Captions and Figures. All pages should be numbered consecutively starting with the title page.

Tables: References to tables should be made in order of appearance in the text and should be in Roman numerals in brackets, e.g. (Table II). Each table should be typed on a separate sheet and have a brief heading describing its contents.

Figures: References to figures should be made in order of appearance in the text and should be in Arabic numerals in parentheses, e.g. (Fig. 2). If a figure has been published before, the original source must be acknowledged and written permission from the copyright holder must be submitted with the material. Patients shown in photographs should have their identity obscured or the picture must be accompanied by written permission to use the photograph.

References: All the references, including those with only electronic sources, should be cited according to the "Vancouver Citation Style" which can be consulted on the Internet at: http://library.vcc.ca/downloads/VCC_VancouverStyleGuide.pdf.

References must be numbered consecutively in the order in which they are cited in the text. Each reference should give the name and initials of all authors unless they are more than six, when only the first three should be given followed by *et al*. Authors' names should be followed by the title of the article, journal abbreviations according to the style used in *Index Medicus*, the year of publication, the volume number and the first and last page numbers. References to books should contain the title of the book, followed by place of publi cation, publisher, year, and relevant pages.

Examples

1. Journals:

Brenninkmeijer L, Eitner F, Floege J. How to write and publish a scientific paper.Port J Nephrol Hypert 2012;26(4):239-244

2. Books by a single author:

Botella García J. Manual de Nefrología Clínica. 1st ed. Barcelona: Masson SA, 2003:209

3. Chapters:

Carrera F, Frazão JM. Thromboembolism and atheroembolic disease of the kidney. In: Schena, FP, ed. Nephrology. London: McGraw Hill International, 2001:355-359.

End page: The end page should include the sources of any support for the work in the form of grants, equipment, drugs, or any combination thereof. Potential conflicts of interest, for example concerning shareholding in or receipt of a grant, consultancy fees or honoraria from industry, should be explicitly stated in line with the ICMJE guidelines II:D1 on individual authors commitment and II:D2 on project support.